PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Assistant Commissioner for Patents
United States Patent and Trademark Office
Box PCT
Washington, D.C.20231
ÉTATS-UNIS D'AMÉRIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 08 December 1999 (08.12.99)	
International application No. PCT/CA99/00314	**Applicant's or agent's file reference** 76023-19
International filing date (day/month/year) 07 April 1999 (07.04.99)	**Priority date** (day/month/year) 07 April 1998 (07.04.98)
Applicant HISCOTT, John et al	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

28 October 1999 (28.10.99)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland**	Authorized officer Marc Salzman
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
76023-19		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/CA99/00314	07/04/1999	07/04/1998
International Patent Classification (IPC) or national classification and IPC C12N15/12		
Applicant THE SIR MORTIMER B. DAVIS-JEWISH GENERAL... et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 5 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which hav been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 13 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
28/10/1999	17.07.00
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Stolz, B Telephone No. +49 89 2399 8416

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/CA99/00314

I. Basis of th r port

1. This report has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

Description, pages:

1-4,6-10,12-41	as originally filed			
5,5a,11,11a	as received on	05/06/2000	with letter of	01/06/2000

Claims, No.:

1-34	as received on	05/06/2000	with letter of	01/06/2000

Drawings, sheets:

1/30-30/30	as originally filed

2. The amendments have resulted in the cancellation of:

☐ the description, pages:
☐ the claims, Nos.:
☐ the drawings, sheets:

3. ☒ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

see separate sheet

4. Additional observations, if necessary:

see separate sheet

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims 2, 4-31
	No:	Claims 1, 3
Inventive step (IS)	Yes:	Claims 2, 6-31
	No:	Claims 1, 3-5
Industrial applicability (IA)	Yes:	Claims 1-31
	No:	Claims

2. Citations and explanations

see separate sheet

1. Basis of the report

1.1. A basis for the amendments to claims 15(b), 27 as far as it relates to hepatitis infection, and claims 32 to 34 could not be found in the application documents as originally filed. Hence, these amendments are deemed to contravene Art. 34(2)(b) PCT. Consequently, this report does not contain a reasoned statement with regard to novelty, inventive step and industrial activity of claims 15 and 27 (both partially) and claims 32 to 34.

Also, a basis for the amendments on p. 5, lines 17 to 21, referring to commercial packages, and on p. 11, lines 19 to 21, referring to proteins of other species, is not apparent.

1.2. Replacement pages 2/13 to 4/13 of the sequence listing have been filed. The amendments concern the numbering of amino acid residues and do not affect the contents of the disclosure.

2. Reasoned statement

2.1. This report has been established under the assumption of valid priority rights. The application describes mutant IRF-3 and IRF-7 proteins yielding increased cytokine gene activation when compared to the activation obtained with native proteins.

2.2. Novelty (Art. 33(2) PCT)

Claims 1 and 3, as presently worded, are insufficiently delimited from the prior art. Claim 1 refers to an "interferon regulatory factor" with at least one modified serine or threonine phospho acceptor site in the "carboxy terminus domain". In view of Yoneyama et al., 1998 (cited in the ISR), IRF-3 phosphorylated on Ser 385 or Ser 386 was excluded from the scope of protection. However, Yoneyama et al. describe also replacement mutants where six of the seven Ser have been replaced by Ala (p. 1090, top left). These mutants are within the scope of claims 1 and 3.

The remaining claims cover subject matter which has not been disclosed in the cited prior art.

2.3. Inventive step (Art. 33(3))

Yoneyama et al. disclosed phosphorylation on two serine residues of IRF-3 as a way of activating interferon genes. They also speculated on a potential role in growth regulation. In view of this document, the present contribution can be identified as the provision of IRF analogues. Since these mutants display a surprisingly large stimulation (activity) and the role of additional Ser and Thr residues could not be derived from the cited prior art in an obvious way, inventive step can be acknowledged.

However, claims 4 and 5, as presently worded, are deemed to lack inventive step. These claims include wild-type IRF-7 in phosphorylated form because the term "modification" does not necessarily imply amino acid replacement. As phosphorylation of IRF-3 was known in the art (Yoneyama et al.) and as the IRFs are to a certain degree related, isolation of the corresponding phosphorylated forms of IRF-7 would not have required inventive skills.

E.P.O. PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	**FOR FURTHER ACTION** see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
76023-19		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/CA 99/ 00314	07/04/1999	07/04/1998

Applicant

THE SIR MORTIMER B. DAVIS-JEWISH GENERAL HOSPITAL

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 5 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

[ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

[X] contained in the international application in written form.

[X] filed together with the international application in computer readable form.

[ ] furnished subsequently to this Authority in written form.

[ ] furnished subsequently to this Authority in computer readble form.

[ ] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

[ ] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [X] **Certain claims were found unsearchable** (See Box I).

3. [ ] **Unity of invention is lacking** (see Box II).

4. With regard to the **title,**

[X] the text is approved as submitted by the applicant.

[ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract,**

[X] the text is approved as submitted by the applicant.

[ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. 14

[X] as suggested by the applicant. [ ] None of the figures.

[ ] because the applicant failed to suggest a figure.

[ ] because this figure better characterizes the invention.

INTERNATIONAL SEARCH REPORT

ernational application No.
PCT/CA 99/ 00314

Box I Observations where certain claims were found uns archable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claims 21-22 (as far as they concern an in vivo method) and claims 23-34 are directed to a method of treatment of the human/animal body (rule 39.1 (IV) PCT, the search been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/CA 99/00314

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C12N15/12 C07K14/47 A61K38/17 A61K48/00 C07K19/00
C12N15/62

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C12N C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	MITSUTOSHI YONEYAMA ET AL: "Direct triggering of the type I interferon systemby virus infection: activation of a transcription factor complex containing IRF-3 and CBP/p300" EMBO JOURNAL., vol. 17, no. 4, 16 February 1998 (1998-02-16), pages 1087-1095, XP002110452 OXFORD UNIVERSITY PRESS, SURREY., GB ISSN: 0261-4189 page 1089, right-hand column, paragraph 2 - page 1090 page 1089, left-hand column, paragraph 3 - right-hand column, paragraph 1 figure 4A --- -/--	1,3,15, 16,21,22

[X] Further documents are listed in the continuation of box C.

[ ] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
2 August 1999	17/08/1999

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Le Cornec, N

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	WEI-CHUN AU ET AL: "Identification of a member of the interferon regulatory factor family that binds to the interferon-stimulated response element and activates expression of interferon-induced genes " PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF USA., vol. 92, December 1995 (1995-12), pages 11657-11661, XP000490487 NATIONAL ACADEMY OF SCIENCE. WASHINGTON., US ISSN: 0027-8424 cited in the application the whole document	15,16,18
A	---	21,22
X	L. ZHANG ET AL: EMBL DATABASE ENTRY HSU53830, ACCESSION NUMBER U53830, 19 May 1997 (1997-05-19), XP002110966 cited in the application abstract -& L. ZHANG ET AL: "IRF-7, a new Interferon Regulatory Factor associated with Epstein -Barr virus latency" MOLECULAR AND CELLULAR BIOLOGY., vol. 17, no. 10, October 1997 (1997-10), pages 5748-5737, XP002110967 AMERICAN SOCIETY FOR MICROBIOLOGY, WASHINGTON., US ISSN: 0270-7306	15,17,18
X	--- A. GROSSMAN ET AL: "Characterization of IRF-7, a novel Interferon Regulatory Factor " EMBL DATABASE ENTRY HSU73036, ACCESSION NUMBER U73036 , 21 October 1996 (1996-10-21), XP002110973 cited in the application abstract & UNPUBLISHED,	15,17,18
P,X	--- R. LIN ET AL: "Virus-dependent phosphorylation of the IRF-3 transcription factor regulates nuclear translocation, transactivation potential, and proteasome mediated degradation" MOLECULAR AND CELLULAR BIOLOGY., vol. 18, no. 5, May 1998 (1998-05), pages 2986-2996, XP002110454 AMERICAN SOCIETY FOR MICROBIOLOGY, WASHINGTON., US ISSN: 0270-7306 the whole document	1-9,15, 16,19, 21,22
	--- -/--	

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
P,X	R. LIN ET AL: "Essential role of interferon regulatory factor 3 in direct activation of RANTES chemokine transcription" MOLECULAR AND CELLULAR BIOLOGY., vol. 19, no. 2, February 1999 (1999-02), pages 959-966, XP002110455 AMERICAN SOCIETY FOR MICROBIOLOGY, WASHINGTON., US ISSN: 0270-7306 the whole document	1-9,15, 16,19-22
T	R. LIN ET AL: "Structural and functional analysis of interferon regulatory factor-3: Localization of the Transactivation and autoinhibitory domains" MOLECULAR AND CELLULAR BIOLOGY., vol. 19, no. 4, April 1999 (1999-04), pages 2465-2474, XP002110456 AMERICAN SOCIETY FOR MICROBIOLOGY, WASHINGTON., US ISSN: 0270-7306	

PATENT COOPERATION TREA

by fax and post

PCT

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

MORROW, Joy D.
SMART & BIGGAR
P.O. Box 2999, Station D
900-55 Metcalfe Street
Ottawa, Ontario K1P 5Y6
CANADA

FAX NO: 613-232-8440

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT
(PCT Rule 71.1)

Date of mailing *(day/month/year)*	17.07.00
Applicant's or agent's file reference	IMPORTANT NOTIFICATION
76023-19	

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/CA99/00314	07/04/1999	07/04/1998

Applicant
THE SIR MORTIMER B. DAVIS-JEWISH GENERAL... et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/	Authorized officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	~~Faux, K~~ Stefanie Büchler Tel.+49 89 2399-8062

Form PCT/IPEA/416 (July 1992)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/CA99/00314

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims 2, 4-31
	No:	Claims 1, 3
Inventive step (IS)	Yes:	Claims 2, 6-31
	No:	Claims 1, 3-5
Industrial applicability (IA)	Yes:	Claims 1-31
	No:	Claims

2. Citations and explanations

see separate sheet

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/CA99/00314

I. Basis of the report

1. This report has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

Description, pages:

1-4,6-10,12-41	as originally filed			
5,5a,11,11a	as received on	05/06/2000	with letter of	01/06/2000

Claims, No.:

1-34	as received on	05/06/2000	with letter of	01/06/2000

Drawings, sheets:

1/30-30/30	as originally filed

2. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

3. ☒ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

see separate sheet

4. Additional observations, if necessary:

see separate sheet

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
76023-19		
International application No. PCT/CA99/00314	International filing date *(day/month/year)* 07/04/1999	Priority date *(day/month/year)* 07/04/1998
International Patent Classification (IPC) or national classification and IPC C12N15/12		
Applicant THE SIR MORTIMER B. DAVIS-JEWISH GENERAL... et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 5 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 13 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
28/10/1999	17.07.00
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Stolz, B Telephone No. +49 89 2399 8416

Form PCT/IPEA/409 (cover sheet) (January 1994)

1. Basis of the report

1.1. A basis for the amendments to claims 15(b), 27 as far as it relates to hepatitis infection, and claims 32 to 34 could not be found in the application documents as originally filed. Hence, these amendments are deemed to contravene Art. 34(2)(b) PCT. Consequently, this report does not contain a reasoned statement with regard to novelty, inventive step and industrial activity of claims 15 and 27 (both partially) and claims 32 to 34.

Also, a basis for the amendments on p. 5, lines 17 to 21, referring to commercial packages, and on p. 11, lines 19 to 21, referring to proteins of other species, is not apparent.

1.2. Replacement pages 2/13 to 4/13 of the sequence listing have been filed. The amendments concern the numbering of amino acid residues and do not affect the contents of the disclosure.

2. Reasoned statement

2.1. This report has been established under the assumption of valid priority rights. The application describes mutant IRF-3 and IRF-7 proteins yielding increased cytokine gene activation when compared to the activation obtained with native proteins.

2.2. Novelty (Art. 33(2) PCT)

Claims 1 and 3, as presently worded, are insufficiently delimited from the prior art. Claim 1 refers to an "interferon regulatory factor" with at least one modified serine or threonine phospho acceptor site in the "carboxy terminus domain". In view of Yoneyama et al., 1998 (cited in the ISR), IRF-3 phosphorylated on Ser 385 or Ser 386 was excluded from the scope of protection. However, Yoneyama et al. describe also replacement mutants where six of the seven Ser have been replaced by Ala (p. 1090, top left). These mutants are within the scope of claims 1 and 3.

The remaining claims cover subject matter which has not been disclosed in the cited prior art.

2.3. Inventive step (Art. 33(3))

Yoneyama et al. disclosed phosphorylation on two serine residues of IRF-3 as a way of activating interferon genes. They also speculated on a potential role in growth regulation. In view of this document, the present contribution can be identified as the provision of IRF analogues. Since these mutants display a surprisingly large stimulation (activity) and the role of additional Ser and Thr residues could not be derived from the cited prior art in an obvious way, inventive step can be acknowledged.

However, claims 4 and 5, as presently worded, are deemed to lack inventive step. These claims include wild-type IRF-7 in phosphorylated form because the term "modification" does not necessarily imply amino acid replacement. As phosphorylation of IRF-3 was known in the art (Yoneyama et al.) and as the IRFs are to a certain degree related, isolation of the corresponding phosphorylated forms of IRF-7 would not have required inventive skills.

phosphoacceptor site in the carboxy-terminus domain, preferably wherein cytokine gene activation by the modified IRF is increased relative to cytokine gene activation by a corresponding wild type IRF protein.

The present invention also provides a pharmaceutical composition comprising an effective amount of the interferon regulatory factor (IRF) protein according to the invention, together with a pharmaceutically acceptable carrier, for the treatment of a viral infection, for example, an influenza infection, a herpes infection or an HIV infection.

The present invention further provides use of the interferon regulatory factor (IRF) protein according to the invention to activate a cytokine gene, preferably wherein the cytokine gene is an interferon gene or a chemokine gene.

DESCRIPTION OF THE FIGURES

Figure 1. Sendai virus infection induces IRF-3 degradation.

IRF-3 expression plasmid CMVBL-IRF3 (lanes 1 and 2) or CMVBL vector alone (lanes 3 and 4), both at 5 μg were transiently transfected into 293 cells by the calcium phosphate method. At 24h post transfection, cells were infected with Sendai virus for 16h (lanes 2 and 4) or left uninfected (lanes 1 and 3). Whole cell extracts (20 μg) were prepared and analyzed by immunoblotting with anti-IRF-3 antibody.

Figure 2. Sendai virus induced phosphorylation and degradation of IRF-3 protein.

A) rtTA-IRF-3 cells, selected as described in the Example, were induced to express IRF-3 by doxycycline treatment for 24h. At 24h after Dox addition, cells were infected with Sendai virus for 4, 8, 12, 16, 20, or 24h (lanes 2-7) or were left uninfected (lane 1). IRF-3 protein was detected in whole cell extracts (10 μg) by immunoblot. Two forms of IRF-3 were detected, designated as form I and form II.

B) At 24h post Dox induction, rtTA-IRF-3 cells were infected with Sendai virus for 16 hours (lanes 4-8) or were left uninfected (lanes 1-3). Whole cell extracts from untreated

having aspartic acid residues in at least one of postions 396, 398, 402, 404 and 405 of the sequence, more preferably in positions 396, 398, 402, 404 and 405 of the sequence (IRF-3(5D)) (Figure 10). The preferred mutant form of IRF-7 is that having aspartic acid residues in at least one of positions 477 and 479 of the sequence, more preferable in positions 477 and 479 of the sequence (IRF-7(2D)) (Figure 12).

Also within the scope of the invention are chimeric proteins comprising a carboxy-terminus domain of one modified IRF protein, modified as discussed above, and an amino-terminal domain of another IRF protein. Preferably, the amino-terminus of IRF-7 is fused to the carboxy-terminus of modified IRF-3. It is more preferred that the carboxy-terminus of modified IRF-3 is that of IRF-3(5D). Even more preferred is a chimeric protein comprising residues 1 to 246 of IRF-7 and residues 132 to 427 of IRF-3(5D) (Figure 13).

Also within the scope of the invention are proteins which are substantially homologous to the above proteins and which retain the function of those proteins.

Nucleotide sequences within the scope of the invention are those which encode a protein of the invention. Preferably, the nucleotide sequence is a coding DNA sequence as defined in Figure 10 or a DNA sequence which is hybridizable under stringent conditions with the complement of the coding DNA sequence of Figure 10, which DNA encodes IRF-3(5D). Also, preferably, the nucleotide sequence is a coding DNA sequence as defined in Figure 12 or a DNA sequence which is hybridizable under stringent conditions with the complement of the coding DNA sequence of Figure 12, which DNA encodes IRF-7(2D). Also preferably, the nucleotide sequence is a coding DNA sequence as defined in Figure 13 or a DNA sequence which is hybridizable under stringent conditions with the complement of the coding DNA sequence of Figure 13, which DNA encodes IRF-7(1-246)/IRF-3(132-427) chimeric protein.

A combination of IRF-3 deletion and point mutations localized the inducible phosphorylation sites to the region -ISNSHPLSLTSDQ- between amino acids 395 and 407; point mutation

Claims:

1. A modified interferon regulatory factor (IRF) protein, the protein comprising at least one modified serine or threonine phosphoacceptor site in the carboxy-terminus domain.

2. The interferon regulatory factor (IRF) protein according to claim 1, wherein cytokine gene activation by the modified IRF is increased relative to cytokine gene activation by a corresponding wild type IRF protein.

3. The interferon regulatory factor (IRF) protein according to claim 1 or 2, wherein the at least one modified phosphoacceptor site is modified by phosphorylation.

4. The interferon regulatory factor (IRF) protein according to claim 1 or 2, wherein the at least one modified phosphoacceptor site comprises an amino acid residue having an acidic side chain.

5. The interferon regulatory factor (IRF) protein according to claim 4, wherein the amino acid residue is aspartic acid.

6. The interferon regulatory factor (IRF) protein according to claim 3, 4 or 5, wherein the modified IRF is IRF-3 modified at a site selected from at least one of Ser-396, Ser-398, Ser-402, Thr-404 and Ser-405.

7. The interferon regulatory factor (IRF) protein according to claim 6, wherein the modified IRF is IRF-3 modified at Ser-396, Ser-398, Ser-402, Thr-404 and Ser-405 sites.

8. The interferon regulatory factor (IRF) protein according to claim 7 having the sequence of ID No. 2 in the sequence listing (IRF-3(5D)).

9. The interferon regulatory factor (IRF) protein according to claim 7, wherein the modified IRF comprises a carboxy-terminus domain of IRF-3 modified at a site selected from at least one of Ser-396, Ser-398, Ser-402, Thr-404 and Ser-405 and an amino-terminus domain from IRF-7.

10. The interferon regulatory factor (IRF) protein according to claim 9, wherein the modified IRF has an amino-terminal domain comprising residues 1 to 246 of IRF-7 and a carboxy-terminal domain comprising residues 132 to 427 of IRF-3 modified by replacement of each of Ser-396, Ser-398, Ser-402, Thr-404 and Ser-405 by an aspartic acid residue.

11. The interferon regulatory factor (IRF) protein according to claim 10 having the sequence of ID No. 11 in the sequence listing (IRF-7(1-246)/IRF-3(5D)(132-427)).

12. The interferon regulatory factor (IRF) protein according to claim 3, 4 or 5, wherein the modified IRF is IRF-7 modified at a site selected from at least one of Ser-477 and Ser-479.

13. The interferon regulatory factor (IRF) protein according to claim 12, wherein the modified IRF-7 is modified at Ser-477 and Ser-479 sites.

14. The interferon regulatory factor (IRF) protein according to claim 13 having the sequence of ID No. 9 in the sequence listing (IRF-7(2D)).

15. A nucleotide sequence which encodes the interferon regulatory factor (IRF) protein according to any one of claims 1 to 14, or a nucleotide sequence that is hybridizable under stringent conditions with the complement of the nucleotide sequence which encodes the interferon regulatory factor (IRF) protein.

16. The nucleotide sequence according to claim 15, which is a DNA sequence of ID No. 1 in the sequence listing.

17. The nucleotide sequence according to claim 15, which is a DNA sequence of ID No. 8 in the sequence listing.

18. The nucleotide sequence according to claim 15, which is a DNA sequence of ID No. 10 in the sequence listing.

19. A pharmaceutical composition comprising an effective amount of the interferon regulatory factor (IRF) protein according to any one of claims 1 to 14, together with a pharmaceutically acceptable carrier, for the treatment of a viral infection.

20. The pharmaceutical composition according to claim 19, wherein the viral infection is selected from an influenza infection, a herpes infection and an HIV infection.

21. Use of the interferon regulatory factor (IRF) protein according to any one of claims 1 to 14 to activate a cytokine gene.

22. The use according to claim 21, wherein the cytokine gene is an interferon gene or a chemokine gene.

23. Use of the interferon regulatory factor (IRF) protein according to any one of claims 1 to 14 in cancer treatment.

24. Use of the nucleotide sequence according to any one of claims 15 to 18 to modify a target cell of an organism.